REMARKS

The Claim Amendments

In order to advance prosecution, Applicants have amended claim 36 and dependent claims 38, 48-59, and 68-69 and have canceled claims 37, 39-47, and 60-67. Claims 1-35 were previously canceled. Specifically, claim 36 has been amended to recite a chemically modified double stranded short interfering ribonucleic acid (siRNA) molecule comprising a sense strand and an antisense strand, wherein: the antisense strand of said siRNA molecule comprises about 18 to about 27 nucleotides that are complementary to a platelet-derived endothelial cell growth factor (ECGF1) nucleotide sequence corresponding to SEQ ID NO:225 and are also complementary to the sense strand; the sense strand of said siRNA molecule comprises a portion of said ECGF1 nucleotide sequence of about 18 to about 27 nucleotides; and said siRNA molecule comprises at least one 2'-O-methyl or 2'-deoxy-2'-fluoro nucleotide. Support for the amendments to claim 36 can be found, *inter alia*, at pages 7-10 (chemically modified siRNA, sense strand and antisense strand, antisense strand complementarity to ECGF1 sequence, sense strand comprising a portion of ECGF1 sequence), page 12 (2'-O-methyl and 2'-deoxy-2'-fluoro modifications), page 28 (about 18 to about 27 nucleotides in length), pages 51, 62, 66, and 136 (referring to GenBank Accession No. NM_001953, SEQ ID NO:225). Claim 36 and dependent claims 38, 48-59, and 68-69 have been amended to recite the term "siRNA" rather than "siNA". Support for these amendments can be found, *inter alia*, at pages 1, 7, 62 and throughout the specification. Claims 48, 51-54, 56-59 and 68 have been amended to recite the term "strand" instead of "region". Support for these amendments can be found, *inter alia*, at pages 10, 12-14, and throughout the application. Claims 51-53, and 56-58 have been amended to recite the term "one or more". Support for these amendments can be found, inter alia, at pages 21-22, 26, and 32-39. Claim 68 has been amended to recite the term "terminal" with regard to the claimed phosphate group. Support for this amendment can be found, *inter alia*, at page 24. Claim 69 has been amended to recite the term "pharmaceutically acceptable carrier or diluent". Support for the amendment can be found, *inter alia*, at pages 53-54.

Amendments to the claims are made without prejudice and do not constitute amendments to overcome any prior art or other statutory rejections and are fully supported by the specification as filed. Additionally, these amendments are not an admission regarding the patentability of subject matter of the canceled or amended claims and should not be so construed. Applicant reserves the right to pursue the subject matter of the previously filed claims in this or in any other appropriate patent application. The amendments add no new matter and applicants respectfully request their entry.

The Sequence Listing

Applicants have enclosed a new sequence listing and request its entry in place of the previously entered sequence listing. The sequence listing adds SEQ ID NO: 225. The sequence represents GenBank entry NM_001953 (see Tables I and II). Applicant submits that the CD-R submitted in lieu of the paper copy and the CD-R submitted for the computer-readable copy are identical in content. The sequence listing adds no new matter and applicants respectfully request its entry.

Priority

The Office Action alleges that the instant application is not entitled to the priority date of the prior Provisional Applications because "the Provisional Applications do not disclose siNA targeted to a gene encoding ECGF1" (see Office Action at page 2). The Applicant respectfully disagrees with the Office's assessment of the priority claim because the instant application claims priority, *inter alia*, to U.S. Provisional Application 60/363,124 filed on March 11, 2002 (the '124 application). The '124 application discloses the instantly claimed target, ECGF1, for example, at page 341 (entry for NM_001953, Homo sapiens endothelial cell growth factor 1 (platelet-derived) (ECGF1), mRNA), which is now included in amended Claim 36 as SEQ ID NO:225.

The claims presented above all find complete support in the '124 application. In particular, amended claim 36 finds support for chemically modified double stranded siRNA at p. 3, lines 15-17; p. 6, lines 19-24; and p. 24, lines 22-24; comprising a sense

strand and an antisense strand at p. 7, lines 9-11; each strand is about 18 to about 27 nucleotides in length at p. 12, lines 4-12; complementarity between the sense and antisense strands at p. 12, lines 4-7, and p. 25, lines 17-29; the antisense strand having between 18-27 nucleotides complementary to ECGF1 nucleotide sequence corresponding to SEQ ID NO:225 at p. 18, lines 1-5, p. 12, line 6, p. 341, entry in Table III for GenBank Accession No. NM_001953; sense strand comprising a portion of ECGF1 sequence at p. 15, lines 17-19 and 30-31; and 2'-O-methyl or 2'-deoxy-2'-fluoro modifications at p. 5, lines 13-22; p. 6, line 19 to page 7, line 18 (where R3 of Formula II is F or O-alkyl); and pages 10-11.

Support for the dependent claims can also be found in the '124 application:

Claim	Support
38	One or more ribonucleotides: p. 15, lines 3-9
48	Sense strand connected to antisense strand via linker molecule: p. 19, lines 20-21, 25, 28, p. 20 line 15, p. 38 lines 17-29
49	Polynucleotide linker: p 12, lines 13-26, p. 38, lines 18-29
50	Non-nucleotide linker: p 12, lines 13-26
51	One or more pyrimidine nucleotides present in the sense strand are 2'-O-methyl pyrimidine nucleotides: p. 10, lines 11-13
52	One or more purine nucleotides present in the sense strand are 2'-deoxy purine nucleotides: p. 6, lines 19-23
53	One or more pyrimidine nucleotides present in the sense strand are 2'-deoxy-2'-fluoro pyrimidine nucleotides: p. 10, lines 11-13
54	Sense strand includes a terminal cap moiety at the 5'-end, the 3'-end, or both of the 5' and 3' ends of the sense strand: p. 10, lines 6-7, 20-21, p. 40, lines 1-18
55	Terminal cap moiety is inverted deoxy abasic moiety: p. 5, line 16, p. 14, lines 10-13, p. 40, lines 4-18.
56	One or more pyrimidine nucleotides present in the antisense strand are 2'-deoxy-2'-fluoro pyrimidine nucleotides: p. 10, lines 11-13
57	One or more purine nucleotides in antisense strand are 2'-O-methyl purine nucleotides: p. 6, lines 19-25
58	One or more purine nucleotides present in the antisense strand are 2'-deoxy purine nucleotides: p. 6, lines 19-23

Claim	Support
59	Terminal phosphorothioate internucleotide linkage at 3' end of antisense strand: p. 9, lines 24-25
68	Terminal phosphate group: p. 8, line 26 to p. 9, line 13
69	Composition comprising the double stranded nucleic acid molecule in a pharmaceutically acceptable carrier or diluent: p. 18, lines 15-19

As discussed, support for all of the pending claims can be found in the 60/363,124 application. The instant application claims priority to and incorporates by reference PCT/US03/05346 in its entirety, which application claims priority to and incorporates by reference 60/363,124 in its entirety. Thus, the instant application properly claims priority to the 60/363,124 application. Applicant respectfully submits that the instant invention is entitled to a priority date of at least March 11, 2002, the filing date of the 60/363,124 application.

Obviousness-Type Double Patenting Rejection

Claims 36-69 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being obvious over claims 1-35 of copending Application No. 10/922,034.

Without acceding to the merits of the rejection, Applicant will consider filing a terminal disclaimer upon allowance of the pending claims.

35 U.S.C. § 112 Second Paragraph, Rejections

Claim 48 was rejected under 35 U.S.C. 112 second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention because the limitation "wherein said sense region" allegedly lacks antecedent basis. Claim 48 depends from claim 36, which recites the term "sense strand". Claim 48 has been amended to recite "sense strand" rather than "sense region", thus providing the proper antecedent basis. According, Applicant respectfully requests withdrawal of the 35 U.S.C. § 112 second paragraph rejection with respect to claim 48.

Claims 51, 53, and 56 were rejected under 35 U.S.C. 112 second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention because the limitation "wherein pyrimidine nucleotides" allegedly lacks antecedent basis. Claims 51, 53, and 56 have been amended to recite the phrase "wherein one or more pyrimidine nucleotides present in the sense [or said antisense] strand". Applicant believes such language clarifies the subject matter of the claims. According, Applicant respectfully requests withdrawal of the 35 U.S.C. § 112 second paragraph rejection with respect to these claims.

Claims 52, and 57-58 were rejected under 35 U.S.C. 112 second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention because the limitation "wherein purine nucleotides present in the sense [or said antisense] strand" allegedly lacks antecedent basis. Claims 52, and 57-58 have been amended to recite the phrase "wherein one or more purine nucleotides present in the sense [or said antisense] strand". Applicant believes such language clarifies the subject matter of the claims. According, Applicant respectfully requests withdrawal of the 35 U.S.C. § 112 second paragraph rejection with respect to these claims.

Claims 59-60 were rejected under 35 U.S.C. 112 second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention because the limitation "wherein said sense region" allegedly lacks antecedent basis. Claim 60 has been canceled, thus rendering the rejection moot as applied to this claim. Claim 59, which depends from claim 36, has been amended to recite "sense strand" rather than "sense region" because the term "sense strand" is found in claim 36, thus providing proper antecedent basis. According, Applicant respectfully requests withdrawal of the 35 U.S.C. § 112 second paragraph rejection with respect to claim 59.

Claims 62 and 66 were rejected under 35 U.S.C. 112 second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter

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which applicant regards as the invention because the limitation "wherein about 19 nucleotides" allegedly lacks antecedent basis. Claims 62 and 66 have been canceled, thus rendering the rejection moot as applied to these claims.

Accordingly, Applicant respectfully requests withdrawal of the 35 U.S.C. § 112 second paragraph rejections.

35 U.S.C. § 103 Rejections

Claims 36-46 and 51-69 were rejected under 35 U.S.C. 103(a) as being unpatentable over Wyatt *et al.* (U.S. Patent No. 6,716,975), Hammond *et al.* (Nature, 2001, Vol. 2, pages 110-119), Tuschl *et al.* (WO 02/44321), Parrish *et al.* (Molecular Cell, 2000, Vol. 6, pages 1077-1087), and Cook *et al.* (U.S. Patent No. 5, 587,471). Claims 37, 40-46, and 60-67 have been canceled, thus rendering the rejection moot as applied to these claims. Applicants respectfully traverse the rejection with respect to claims 36, 38, 51-59, and 68-69.

Applicants submit that the Office Action has not established a *prima facie* case of obviousness. To establish a *prima facie* case of obviousness three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the references, when combined must teach or suggest all the claim limitations. *See* MPEP §2143.

In the present case, there is no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine reference teachings to arrive at the presently claimed invention. There must be some reason, suggestion, or motivation found in the cited references whereby a person of ordinary skill in the field of the invention would make the substitutions required. That knowledge cannot come from the applicants' disclosure of the invention itself. *Diversitech Corp. v. Century Steps, Inc.*, 7 U.S.P.Q.2d 1315,1318

(Fed. Cir. 1988); *In re Geiger*, 2 U.S.P.Q.2d 1276, 1278 (Fed. Cir. 1987); *Interconnect Planning Corp. v. Feil*, 227 U.S.P.Q. 543, 551 (Fed. Cir. 1985).

An examiner can satisfy the burden required for obviousness in light of combination "only by showing some objective teaching [leading to the combination]." *See, In re Fritch*, 972 F.2d 1260, 1265, 23 U.S.P.Q.2d 1780, 1783 (Fed. Cir. 1992). Evidence of the teaching or suggestion is "essential" to avoid hindsight. *In re Fine*, 837 F.2d 1071, 1075, 5 U.S.P.Q.2d 1596, 1600 (Fed. Cir.1988). Combining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability--the essence of hindsight. *See, e.g., Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1138, 227 U.S.P.Q. 543, 547 (Fed. Cir. 1985). "Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references." *In re Dance*, 160 F.3d 1339, 1343, 48 U.S.P.Q.2d 1635, 1637 (Fed. Cir. 1998). The need for specificity is important. *See, e.g., In re Kotzab*, 217 F.3d 1365, 1371, 55 U.S.P.Q.2d 1313, 1317(Fed. Cir. 2000) ("particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed").

The Applicant submits that one of skill in the art would not have been motivated to combine the cited references to arrive at the presently claimed invention. Tuschl is the only reference cited that teaches a structure of the claimed nucleic acid molecules, *i.e.*, a short double stranded RNA molecule having one strand complementary to a target RNA and another strand having sequence comprising a portion of the target RNA sequence. All of the other references describe either long double stranded RNA (Hammond, Parrish), or antisense art (Wyatt *et al.* and Cook *et al.*). Although long double stranded RNA and antisense are nucleic acid based technologies, they differ substantially from the present invention both mechanistically and structurally, particularly in relation to the chemical modification strategies that allow such molecules to remain active. Just as

antisense modifications are not amenable to long double stranded RNA and vice versa, neither of these nucleic acid technologies provides any insight or guidance into chemical modification of the siRNAs as described by Tuschl.

The Office Action states that "Tuschl *et al.*, Parrish *et al.* and Cook *et al.* provide motivation to incorporate chemical modifications into a dsRNA because the modifications are important for mediating RNA interference and important for the molecules stability" (see Office Action at page 8). However, as is described below, the prior art provides insufficient basis for the ordinary artisan to have had a reasonable expectation that the claimed double stranded RNA molecules would have the properties of inducing RNAi as effectively disclosed by the present applicants, and, indeed, the prior art provides teachings away from the claimed molecules.

The Office Action states that "Parrish *et al.* teach a siRNA with an antisense or sense region comprising 2'-deoxy'2-fluoro pyrimidine nucleotides (see Figure 5) and further teach this siRNA can mediate degradation of cellular RNA" (see Office Action at pages 7 and 11). However, the Parrish *et al.* reference does not teach modified siRNA, as all of the modified constructs tested by Parrish *et al.* were long double stranded RNAs (as described below) that were prepared using enzymatic methods. The paper by Parrish represents a broad survey of the biochemical properties of the RNAi reaction in nematodes using long dsRNAs, but it does not provide any useful information regarding the design of modified siRNA molecules, including chemicall modified siRNA. In 2000–2001 it was clear that RNAi was a conserved cellular mechanism that was present in a diverse set of organisms; it was first discovered in plants, then in nematodes, ciliates, fungi, Drosophila, and finally in mammalian cells (see for example Tuschl et al). But while the basic mechanism is conserved, it was clear to those skilled in the art that the mechanistic details could be very different from one organism to another. Specifically, the lower Eukaryotes are easily activated by long dsRNA, while publications such as Elbashir *et al.*, 2001, EMBO J., Vol 20, No. 23, pages 6877-6888, noted that long dsRNA failed to stimulate RNAi in mammalian cells; this was likely due to the activation of an interferon response in mammalian cells, which is absent in the lower Eukaryotes.

Likewise, Bernstein et al (2001, *RNA* 7:1509-1521) noted that *C. elegans* and plants have a number of RNAi-related behaviors that are not found in mammalian cells, including the ability to pass the RNAi effect from one cell to the next, the ability to amplify the RNAi response such that a few dsRNA molecules can elicit a potent RNAi response, and the ability to pass the RNAi response from one cell generation to the next due to the long-lived nature of RNAi in these organisms (p1515-1516). These profound differences would teach those skilled in the art that it is unwise to generalize discoveries made in *C. elegans* to the world of mammalian RNAi.

A second factor that makes it difficult to draw lessons from Parrish *et al.* is that all of the studies were performed using long dsRNA. The shortest dsRNA molecules used were 26 & 27 bp, but these were only used for initial base composition studies and not for chemical modification studies. In fact, Parrish clearly states that any molecules less than 26 bps were inactive (p1079, right column). The nucleotide modification studies were performed primarily using a 742 bp *unc*-22A sequence that apparently also contained "3–30 nt of dsRNA derived from polylinker sequences on each end, and polylinker-derived single stranded tails of 10–30 nt." (Materials & Methods, p1085). The authors checked the annealing of these sequences by agarose gel, but that would only confirm that they were stuck together, not whether they were annealed properly. These long sequences add a great deal of ambiguity to the interpretation of the results. An "inactive" modification could be such because it failed to allow the strands to anneal properly rather than being deleterious to the RNAi machinery, and an "active" modification could actually be an inactive modification that is distributed sparsely enough on the sequence that the RNAi machinery can still function. This latter possibility is of particular concern since Parrish reports that they "were able to demonstrate interference activity following incorporation of any single modified residue", but that "RNAs with two modified bases also had substantial decreases in effectiveness as RNAi triggers." (p1081, right column). Thus, the modifications have a cumulative effect such as would be expected if the RNAi machinery was finding unmodified places on the long dsRNA to bind and activate.

One final argument against Parrish is that they themselves were unable to formulate a cogent conclusion to their chemical modification studies. They tested over 30 combinations of chemical modifications (their Figure 5, Figure 6, and data not shown), but in the discussion section they can only muster three short paragraphs speculating on the possible implications of these studies (p1084, left column). Their conclusions are: (1) the dsRNA might need to maintain an A-form helix to be active, (2) the antisense strand is more sensitive to modification than the sense strand, and (3) some modifications affect RNAi activity when added to either strand. These speculations are only weakly supported by the data. Coupled with the concerns mentioned above regarding long dsRNA and the difficulty of extending observations from *C. elegans* to mammalian cells, these considerations would have made it very difficult for one of skill in the art to draw any conclusions whatsoever from Parrish regarding the design of short siRNA molecules.

Furthermore, the knowledge of one of ordinary skill and the state of the art at the time of filing the present application prevented the inventions claimed in the instant application from being realized. As demonstrated by Tuschl, the results of testing of chemically modified *short double stranded RNA* clearly teach away from the present invention. Tuschl attempted to apply chemical modifications to siRNA based on the teachings of the prior art, including Parrish (see for example Elbashir *et al.*, 2001, Genes and Development, 15:188-200, which was published by the inventors of Tuschl *et al.*, and which references the work of Parrish at page 198), but failed beyond replacing 3'-terminal ribonucleotides with deoxynucleotides. These molecules were found to have significantly diminished activity or were totally inactive in inducing target specific cleavage by RNAi. For example, the discussion of page 46 of Tuschl describes siRNA duplexes having internal base paired modifications (2'-deoxy and 2'-O-methyl) and is reproduced below:

> To assess the importance of the siRNA ribose residues for RNAi, duplexes with 21 nt siRNAs and 2 nt 3'-overhangs with 2'-deoxy- or 2'-O-methyl-modified strands were examined (Figure 4). Substitution of the 2 nt 3'-overhangs by 2'-deoxynucleotides had no effect and even the replacement of two additional ribonucleotides by 2'-deoxyribonucleotides adjacent to the overhangs in the paired region produced significantly

> active siRNAs. Thus, 8 out of 42 nt of the siRNA duplex were replaced by DNA residues without loss of activity. Complete substitution of one or both siRNA strands by 2'-deoxy residues, however, abolished RNAi, as did complete substitution by 2'-O-methyl residues.

Figure 14 of Tuschl clearly shows that only limited 2'-deoxy substitutions at the 3'-end of a siRNA molecule could be tolerated. Importantly, in all cases where substantial internal base paired substitutions were used, such modification was shown not to be tolerated for RNAi. In addition, according to "*The siRNA Users Guide*" on pages 49-50 of Tuschl,

> 2'-deoxy substitutions of the 2 nt 3'-overhanging ribonucleotides do not affect RNAi, but help to reduce the costs of RNA synthesis and may enhance RNase resistance of siRNA duplexes. More extensive 2'-deoxy or 2'-O-methyl modifications reduce the ability of siRNAs to mediate RNAi, probably by interfering with protein association for siRNP assembly.

It is important to understand that because the first sentence quoted above references only 2'-deoxy modifications and not 2'-O-methyl modifications, the term "More extensive" in the second sentence can modify only "2'-deoxy" in the second sentence and not "2-O-methyl." The beginning of the second sentence is equivalent to "2'-O-methyl and more extensive 2'-deoxy modifications reduce the ability of siRNAs to mediate RNAi." Thus, Tuschl flatly states that 2'-O-methyl modifications should be avoided.

The Office action states that "one would expect such modifications would benefit siRNAs because such modifications had been shown to benefit antisense or ribozymes" (see Office Action at page 8). However, based on the teachings of "[t]he siRNA Users Guide" from Tuschl, one of skill in the art would have avoided making any modifications beyond the 2'-deoxynucleotide substitutions at the 3'-end of the siRNA molecule and certainly would not have been motivated to pursue the presently claimed invention, *i.e.*, a chemically modified siRNA molecule having at least one 2'-O-methyl or 2'-deoxy-2'-fluoro nucleotide. How could one have been motivated to make more extensive modifications when the **only** piece of prior art dealing directly with short double stranded RNA molecules expressly states that more extensive modifications result in decreased activity?

This conclusion is further supported by publications in the field in the 2001 and 2002 time frame, where experts in the field followed the teachings of Tuschl (as were published in Elbashir *et al.*, 2001, EMBO J. Vol. 20, No. 23, pages 6877-6888) and designed siRNAs without any modifications other than two deoxythymidine nucleotides at the 3'-end of the siRNA (*see, e.g.,* Bitko *et al.,* 2001, BMC Microbiology, 1, 34 page 9, left column under heading Materials and Methods section; Kumar *et al.*, 2002, Malaria Journal, 1:5, page 9, right column, under heading Transfection by Inhibitory dsRNA"; and Holen *et al.,* 2002, Nucleic Acids Research, 30, 1757-1766, Figures 1, 2 and 6). These prior art references demonstrate that Tuschl taught away from the presently claimed invention and not just from 100% modified duplexes. If it would have been obvious, clearly, the presently claimed invention would have been practiced by those of skill in the art, including Tuschl and those that followed Tuschl's teaching.

The above argument is best explained by a plain reading of Tuschl (and Elbashir *et al.*, *supra*), which teaches that no modifications other than 3'-terminal deoxy nucleotides are not tolerated and likely interfere with protein association in siRNP assembly. As such, Tuschl did not provide any motivation to a person skilled in the art to take the teachings of the prior art, e.g., long dsRNA, antisense or ribozymes, and apply it to short double stranded RNA molecules as presently claimed because Tuschl tried this approach and failed; Tuschl therefore teaches away from using modifications beyond use of 2'-deoxynucleotides at the 3'-terminal positions of the short double stranded RNA molecules and not just 100% modification. One of skill in the art would not have been motivated to incorporate 2'-O-methyl or 2'-deoxy-2'-fluoro modifications within a siRNA molecule as is presently claimed.

Moreover, the cited references, alone or in combination, do not provide a reasonable expectation of success, as is clearly shown from the teachings of Tuschl (via the Elbashir publication) and the state of the art following Tuschl. The existence or lack of a reasonable expectation of success is assessed from the perspective of a person of ordinary skill in the art at the time the invention was made. *See, Micro Chem. Inc. v. Great Plains Chem. Co.,* 103 F.3d 1538, 1547, 41 U.S.P.Q.2d 1236, 1245 (Fed. Cir.

1997). The inventors' ultimate success is irrelevant to whether one of ordinary skill in the art, at the time the invention was made, would have reasonably expected success. *See, Standard Oil Co. v. American Cyanamid Co*, 774 F.2d 448, 454, 227 U.S.P.Q. 293, 297 (Fed. Cir. 1985). It is impermissible to use hindsight. That is, one can not use the inventors' success as evidence that the success would have been expected. *See, In re Kotzab*, 217 F.3d 1365, 1369, 55 U.S.P.Q.2d 1313, 1316, (Fed. Cir. 2000).

Applicant submits that no *prima facie* case of obviousness exists because, as described above, there would have been no motivation to combine the cited references, no reasonable expectation of success in such a combination, and finally, the cited references in combination do not properly teach the presently claimed invention, and in fact, teach against the instant claims. Because no prima facie case of obviousness has been established, the applicant's respectfully submit that the Office has used improper hindsight reasoning in rejecting the claims.

The applicants are the first ones to show that selective incorporation of 2'-O-methyl and 2'-deoxy-2'-fluoro modifications are well tolerated in siRNA molecules targeting gene expression, as evidenced by the fact that the applicants were the first to utilize double stranded nucleic acid molecules as presently claimed to successfully down regulate gene expression. For example, in co-pending application USSN 10/922,034, published as US-2005-0164967-A1, Applicant has designed, synthesized, and tested the presently claimed chemically modified siRNA molecules having potent activity directed against ECGF1 gene expression (see for example Figures 22 and 23 and corresponding descriptions on pages 100 and 150-151). In addition, in co-pending application USSN 10/444,853, published as US-2004-0192626, applicant has designed, synthesized, and tested several 2'-deoxy-2'-fluoro and 2'-O-methyl modified siRNA molecules having potent activity directed against several different gene targets (see for example Figure 6 with a corresponding description on page 28, paragraph [0219], Figure 7, with a corresponding description on page 28, paragraph [0220], both described in Example 5 starting on page 68 and with sequences shown in Table I; see also Figures 11-15). These co-pending applications demonstrate that application of 2'-deoxy-2'-fluoro and 2'-O-

methyl modifications to siRNA structures are well tolerated for maintaining potent RNAi activity against ECGF1 and other target nucleic acid sequences.

For the reasons set forth above, a person skilled in the art would not have been motivated to follow the teachings of Tuschl, let alone Parrish or the antisense art, to make and use the double stranded nucleic acid molecules of the present invention to target human ECGF1 gene expression. Thus, Wyatt *et al.* (U.S. Patent No. 6,716,975), Hammond *et al.* (Nature, 2001, Vol. 2, pages 110-119), Tuschl *et al.* (WO 02/44321), Parrish *et al.* (Molecular Cell, 2000, Vol. 6, pages 1077-1087), and Cook *et al.* (U.S. Patent No. 5, 587,471), alone or in combination, do not render the present claims obvious. Accordingly, Applicant respectfully requests withdrawal of the 35 U.S.C. § 103(a) rejections based on these teachings.

Claims 36-44, 46-59, and 61-69 were rejected under 35 U.S.C. 103(a) as being unpatentable over Wyatt *et al.* (U.S. Patent No. 6,716,975), Hammond *et al.* (Nature, 2001, Vol. 2, pages 110-119), Tuschl *et al.* (WO 02/44321), Parrish *et al.* (Molecular Cell, 2000, Vol. 6, pages 1077-1087), and further in the view of Matulic-Adamic (U.S. Patent No. 5,998,203) and Thomson *et al.* (Nucleic Acids Research 1993). Claims 37, 40-44, 46, 47, and 61-67 have been canceled, thus rendering the rejection moot as applied to these claims. The Applicants respectfully traverse the rejection with respect to claims 36, 38, 48-59 and 68-69.

The Office Action alleges that Matulic-Adamic teaches double stranded structures comprising abasic terminal cap moieties that provide resistance to degradation and also teaches a double stranded structure comprising separate sense and antisense strands wherein the structure comprises a connecting loop comprising a linker or non-nucleotide linker. The Office Action alleges that Thompson teaches a similar structure and further teaches that linkers increase the efficiency of production and enhance stability of the molecule. The Office Action concludes, based on the cited references, that it would have been obvious to one of ordinary skill to make a dsRNA that is 21 nucleotides in length with chemical modifications targeted to a EDG1 gene at taught by the combined

teachings of Wyatt, Tuschl and Parrish and it further would have been obvious to make a dsRNA where the sense and antisense strands are connected by a linker as taught by Matulic Adamic *et al.* and Thompson *et al.*

First, for the reasons stated above, Wyatt, Hammond, Tuschl and Parrish do not teach the presently claimed siRNA molecules. Specifically, the present claims require the siRNA molecule targeted to ECGF1 to contain at least one 2'-O-methyl or 2'-deoxy-2'-fluoro nucleotide. For the previously stated reasons, Wyatt, Tuschl, Hammond, and Parrish, alone or in combination, fail to teach or suggest such modification as applied to siRNA molecules with a reasonable expectation of success.

The Matulic Adamic *et al.* and Thompson *et al.* references fail to cure the deficiencies of Wyatt, Tuschl and Parrish. Although Matulic Adamic *et al.* and Thompson *et al.* teach in general terms sugar modifications and teach generally the use of linkers as applied to ribozyme molecules, neither Matulic Adamic *et al.* nor Thompson *et al.* teach or suggest the incorporation of 2'-O-methyl or 2'-deoxy-2'-fluoro modification at one or more nucleotides in siRNA molecules. The teachings of Matulic Adamic *et al.* and Thompson *et al.* deal exclusively with ribozyme technology. Although ribozyme technology is a nucleic acid based technology, it differs substantially from the present invention both mechanistically and structurally, particularly in relation to the chemical modification strategies that allow such molecules to remain active. Just as antisense modifications are not amenable to ribozymes and vice versa, neither of these nucleic acid technologies provides any insight or guidance into chemical modification of the dsRNAs described by Parrish or Tuschl.

The Office Action further alleges that one skilled in the art would have a reasonable expectation of success based on the combined references because "chemical modifications of an oligonucleotide adding stability and specificity to oligonucleotides were known in the art at the time of [sic] the invention was made. Additionally, one would expect such modifications would benefit siRNAs because such modifications had been shown to benefit antisense or ribozymes". (Office Action, page 12). However, the

Office provides no further explanation or evidence to demonstrate the basis for the naked assertion that one would reasonably expect the same benefits to a siRNA molecule.

In the absence of such evidence, the Examiner's position goes no further than suggesting that it would have been obvious to try the chemical modifications previously used in connection with ribozymes as taught my Matulic-Adamic and Thompson. However, this is not the correct standard for judging obviousness.

Furthermore, in fact, given the state of the art at the time of filing, one would **not** have reasonably expected the same benefits of modification to a siRNA molecule. As discussed above, Tuschl attempted to apply chemical modifications to siRNA based on the teachings of the prior art, such as those modifications taught in Matulic Adamic *et al.* and Thompson *et al.*, but failed beyond replacing 3'-terminal ribonucleotides with deoxynucleotides. As previously explained, Tuschl's siRNA molecules having internal 2'-deoxy substitutions were found to have significantly diminished activity or were totally inactive in inducing target specific cleavage by RNAi. Tuschl's findings were the accepted state of the art at the time of filing, as evidenced by the publications in the field around 2001 and 2002, where experts in the field followed the teachings of Tuschl and designed siRNAs without any modifications other than two deoxythymidine nucleotides at the 3'-end of the siRNA. Thus, one skilled in the art would not have had a reasonable expectation that the modifications described in Matulic Adamic *et al* and Thompson *et al.* could be successfully applied to siRNA molecules.

For the reasons set forth above, Wyatt *et al.*, Hammond *et al.*, Tuschl *et al.*, and Parrish *et al.*, in further view of Matulic-Adamic *et al.* and Thompson *et al.* do not render obvious the presently claimed invention. Accordingly, Applicant respectfully requests withdrawal of the 35 U.S.C. § 103(a) rejections based on these references.

Claims 36-46, 51-53, and 56-69 were rejected under 35 U.S.C. 103(a) as being unpatentable over Meacci *et al.* (Biochem 2002), Hammond *et al.* (Nature, 2001, Vol. 2, pages 110-119), Tuschl *et al.* (WO 02/44321), Parrish *et al.* (Molecular Cell, 2000, Vol. 6, pages 1077-1087), and Cook et al. (U.S. Patent No 5,587,471). Claims 37, 40-44, 46,

47, and 61-67 have been canceled, thus rendering the rejection moot as applied to these claims. The applicants respectfully traverse the rejection with respect to claims 36, 38, 51-53, 56-59, and 68-69.

The Office alleges that Meacci et al. teach a nucleic acid molecule targeted to EDG1 that comprises modified deoxyribonucleotides wherein the nucleic acid molecule is 21 nucleotides in length. The Office expressly states that Meacci et al. do not teach a double-stranded nucleic acid molecule targeted to EDG1 and further do not teach modified nucleotides comprising 2'-deoxy or 2'deoxy-2'fluoro nucleotides or comprise two separate strands connected via a linker molecule. The Office concludes that it would have been obvious to one of ordinary skill in the art to make a dsRNA targeted to EDG1 gene, as taught by Meacci et al. and further it would have been obvious for one of ordinary skill in the art to make a dsRNA which are 21 nucleotides in length with chemical modifications, as taught by Tuschl et al. Parrish et al., and Cook et al.

First, for the reasons stated above, Tuschl, Parrish, and Cook do not teach the presently claimed siRNA molecules. Specifically, the present claims require the siRNA molecule targeted to ECGF1 to contain at least one 2'-O-methyl or 2'-deoxy-2'-fluoro nucleotide. For the previously stated reasons, Tuschl, Parrish, and Cook, alone or in combination, fail to teach or suggest such modification as applied to siRNA molecules with a reasonable expectation of success.

The Meacci *et al.* reference fails to cure the deficiencies of Tuschl, Parrish, and Cook. Meacci *et al.* simply describe antisense oligonucleotides targeting EDG1. The Office admits that Meacci et al. do not teach a double-stranded nucleic acid molecule targeted to EDG1 and further do not teach modified nucleotides comprising 2'-deoxy or 2'deoxy-2'fluoro nucleotides as required by the present claims. Further, the teachings of Meacci *et al.* deal exclusively with antisense technology. Although antisense technology is a nucleic acid based technology, it differs substantially from the present invention both mechanistically and structurally, particularly in relation to the chemical modification strategies that allow such molecules to remain active. Just as antisense modifications are

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not amenable to ribozymes and vice versa, neither of these nucleic acid technologies provides any insight or guidance into chemical modification of the dsRNAs described by Parrish or Tuschl.

The Office Action further alleges that one skilled in the art would have a reasonable expectation of success based on the combined references because Meacci et al. teach antisense molecules can be targeted to an EDG1 gene and regulate gene expression, Tuschl and Parrish teach that making a dsRNA 21 nucleotides in length with chemical modifications is important for mediating RNAi, and Cook et al teach that glyceryl can be incorporated to improve oligonucleotide pharmacokinetics. Further, one would have a reasonable expectation of success because "chemical modifications of an oligonucleotide adding stability and specificity to oligonucleotides were known in the art at the time of [sic] the invention was made. Additionally, one would expect such modifications would benefit siRNAs because such modifications had been shown to benefit antisense or ribozymes". (Office Action, page 16). However, the Office provides no further explanation or evidence to demonstrate the basis for the naked assertion that one would reasonably expect the same benefits to a siRNA molecule.

As discussed above, given the state of the art at the time of filing, one would **not** have reasonably expected the same benefits of modification to a siRNA molecule. Tuschl attempted to apply chemical modifications to siRNA based on the teachings of the prior art, but failed beyond replacing 3'-terminal ribonucleotides with deoxynucleotides. Tuschl's findings were the accepted state of the art at the time of filing, as evidenced by the publications in the field around 2001 and 2002, where experts in the field followed the teachings of Tuschl and designed siRNAs without any modifications other than two deoxythymidine nucleotides at the 3'-end of the siRNA. Thus, one skilled in the art would not have had a reasonable expectation that the modifications described in the antisense and ribozyme art could be successfully applied to siRNA molecules.

For the reasons set forth above, the combined teachings of Meacci *et al.*, Hammond *et al.*, Tuschl *et al.*, Parrish *et al.* and Cook *et al.* do not render obvious the

presently claimed invention. Accordingly, Applicant respectfully requests withdrawal of the 35 U.S.C. § 103(a) rejections based on these references.

Conclusion

In view of the foregoing amendments and remarks, the applicant submits that the claims are in condition for allowance, which is respectfully solicited. If the examiner believes a teleconference will advance prosecution, she is encouraged to contact the undersigned as indicated below.

Respectfully submitted,
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Date: May 19, 2006

By: _____
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